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## In reply

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would be an important step toward personalized blood transfusion. The meta-analysis by Hovaguimian and Myles.<sup>5</sup> has made important progress toward this goal.

### Competing Interests

The authors declare no competing interests.

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### In Reply:

We would like to thank Drs. Warner, Qiu, and colleagues for their valuable inputs regarding our systematic review.<sup>1</sup>

Dr. Warner rightly points out that CIs crossing the equality line correspond to nonsignificant results and suggests that the wording of our findings may have failed to reflect this lack of statistical significance. Although we agree that “borderline” results (*i.e.*, where one end of the CI just overlaps the null value) should be interpreted with caution, it is worth to note that the Cochrane Collaboration discourages formulations such as “nonsignificant” or “not statistically significant,” since these terms are commonly misinterpreted as an indication that “the intervention has no effect.”<sup>2</sup> Although some authors would describe such findings as a “tendency” or a “trend” toward an effect, we opted for a more moderate wording (*i.e.*, using formulations such as “seemed to” or “possible increase”), as suggested elsewhere.<sup>3</sup> As for the interpretation of borderline findings, it might help to remember that the true effect is more likely to lie around the point estimate (*i.e.*, around the

risk ratio) than at the margins of the CI.<sup>3</sup> The traditionally significant  $P < 0.05$  may well be suitable for testing efficacy, but CIs rather than hypothesis testing are preferred when testing safety, equivalence, or noninferiority.<sup>4</sup>

A second concern of Dr. Warner’s is that our analysis did not include transfusion-related pulmonary complications, which may have resulted in an underestimation of potential harmful effects associated with liberal transfusion strategies. The rationale behind the exclusion of pulmonary complications was mainly related to the quality of the reported data in the original trials: in most studies, there was no distinction between transfusion-related events (such as acute lung injury or pulmonary edema due to circulatory overload) and events secondary to inadequate oxygen supply, such as left-sided heart failure due to myocardial infarction. Including outcomes with opposite etiologies could have resulted in a dilution of the intervention effects.

Qui *et al.* highlight a potential issue encountered in trials addressing transfusion strategies, *i.e.*, the fact that heterogeneity in hemoglobin levels within individual treatment groups may potentially dilute treatment effects. Their concern is based on the assumption that patients assigned to a restrictive strategy who received blood transfusions would eventually have the same (posttransfusion) hemoglobin levels as those from the liberal group. A similar issue may occur if some patients assigned to a restrictive strategy never developed anemia (*i.e.*, perioperative hemoglobin levels maintained in the range of the liberal group). This could indeed lead to an underestimation of adverse events, since only a small fraction of patients assigned to a restrictive strategy would truly be at risk of developing anemia-related complications. To address this potential source of heterogeneity, Qui *et al.* propose to stratify the analysis according to hemoglobin levels (see table 1, which provides a detailed description of hemoglobin levels across studies). Although the idea is very elegant, such exploratory analyses should be carried out with caution, since the quality of the reported data remains limited (data not extractable, heterogeneity in the frequency or duration of hemoglobin measurements, or use of inadequate statistics [*e.g.*, Student’s *t* test for data correlated over time]). It is also worth noting that the randomized design used in the original studies tends to protect from bias and residual confounding. We certainly agree that large, well-designed randomized controlled trials are still needed to fully explore the effects of transfusion strategies and eagerly await the results of the ongoing Transfusion Requirements in Cardiac Surgery-III trial (NCT 02042898).

### Competing Interests

The authors declare no competing interests.

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**Table 1.** Hemoglobin Levels across Studies

Study Characteristics			Intervention Characteristics							
Study ID	Setting or Reason for Admission	Hemoglobin Threshold (g/l)		Mean Hemoglobin Levels (g/l)		Corresponding Hematocrit (%)		Mean Hemoglobin/Hematocrit Levels: Number of Measurements and Time Frame	Hemoglobin Levels Differed Significantly Over Time?	
		Restrictive	Liberal	Restrictive	Liberal	Restrictive	Liberal			
Group 1: cardiovascular disease, cardiac/vascular surgery, or interventional catheterization										
Bracey 1999 <sup>47</sup>	Elective cardiac (CABG)	80	90	NE	NE	NE	NE	—	No	
Bush 1997 <sup>48</sup>	Elective vascular (aortic + infrainguinal)	90	100	98	110	29.4	33	6 measurements during 48 h	Yes	
Carson 2013 <sup>6</sup>	Interventional catheterization	S (80)	100	91	106	28.4	31.8	Mean hemoglobin levels at day 3 POP	Yes	
Cooper 2011 <sup>51</sup>	Interventional catheterization or cardiac surgery	80	100	93	102	27.9	30.6	Daily measurements during 14 d	Yes	
Hajjar 2010 <sup>55</sup>	Elective cardiac (CABG, valve)	80	100	91	105	28.4	31.8	6 measurements during 7 d	Yes	
Murphy 2015 <sup>60</sup>	Elective cardiac (CABG, valve, aortic)	75	90	NE	NE	NE	NE	—	Yes	
Shehata 2012 <sup>66</sup>	Elective cardiac (CABG, valve)	70 IOP 75 POP	95 IOP 100 POP	91	107	27.3	32.1	Daily measurements during 6 d	Yes	
Slight 2008 <sup>67</sup>	Elective cardiac (CABG, valve)	RCV schema	80–90	102	102	30.6	30.6	Mean hemoglobin levels at day 6 POP	No	
Group 2: elderly and orthopedic surgery										
Carson 1998 <sup>49</sup>	Hip fracture	S (80)	100	97	107	29.1	32.1	Mean hemoglobin levels at discharge	Yes	
Carson 2011 <sup>50</sup>	Hip fracture	S (80)	100	NE	NE	NE	NE	—	Yes	
Fan 2014 <sup>52</sup>	Elective lower limb joint replacement (hip)	80	100	87	104	26.1	31.2	Mean hemoglobin levels at day 3 POP	Yes	
Foss 2009 <sup>8</sup>	Hip fracture	80	100	NE	NE	NE	NE	—	No	
Gregersen 2015 <sup>9</sup>	Hip fracture	97	113	113	122	33.9	36.6	5 measurements during 30 d	Yes	
Grover 2006 <sup>54</sup>	Elective lower limb joint replacement	80	100	99	111	29.7	33.3	4 measurements during 5 d	Yes	
Nielsen 2014 <sup>62</sup>	Elective hip revision	73	89	102	99	30.6	29.7	Unclear	No	
Parker 2013 <sup>63</sup>	Hip fracture	S	100	112	115	33.6	34.5	Mean hemoglobin levels at 6 wk	NR	
So-Osman 2010 <sup>68</sup>	Elective lower limb joint replacement	Standardized schema	Non standardized	114	114	34.2	34.2	Mean hemoglobin levels at discharge	No	

(Continued)

**Table 1.** (Continued)

Study Characteristics			Intervention Characteristics							
Study ID	Setting or Reason for Admission	Hemoglobin Threshold (g/l)		Mean Hemoglobin Levels (g/l)		Corresponding Hematocrit (%)		Mean Hemoglobin/Hematocrit Levels: Number of Measurements and Time Frame	Hemoglobin Levels Differed Significantly Over Time?	
		Restrictive	Liberal	Restrictive	Liberal	Restrictive	Liberal			
Group 3: mixed medical/surgical cases and acute care										
de Almeida 2015 <sup>7</sup>	Surveillance post major abdominal surgery	70	90	NE	NE	NE	NE	—	Yes	
Fortune 1987 <sup>53</sup>	Trauma or surgical bleeding	100*	133*	101	127	30.3	38.1	NR	Yes	
Hebert 1995 <sup>57</sup>	Various diagnoses	70–75	100–105	90	109	27	32.7	Daily measurements during ICU stay	Yes	
Hebert 1999 <sup>56</sup>	Various diagnoses	70	100	85	107	25.5	32.1	Daily measurements during ICU stay	Yes	
Holst 2014 <sup>58</sup>	Septic shock	70	90	NE	NE	NE	NE	—	Yes	
Jairath 2015 <sup>34</sup>	Upper gastrointestinal bleeding	80	100	115	115	34.5	34.5	Mean hemoglobin levels during the entire study period	No	
Markatou 2012 <sup>59</sup>	Surveillance post major abdominal surgery	77	99	NE	NE	NE	NE	—	Yes	
Topley 1956 <sup>69</sup>	Trauma	70–80% of RCV	Normal RCV	113	156	3.9	46.8	NR	Yes	
Villanueva 2013 <sup>70</sup>	Upper gastrointestinal bleeding	70	90	92	101	27.6	30.3	Daily measurements during hospital stay	Yes	
Walsh 2013 <sup>35</sup>	Various diagnoses	70	90	82	96	24.6	28.8	Daily measurements during ICU stay (maximum 14 d)	Yes	
Group 4: younger, fitter, and brain injury/intracranial bleeding										
Naidech 2010 <sup>61</sup>	Neuro-ICU	100	115	NE	NE	NE	NE	—	Yes	
Robertson 2014 <sup>65</sup>	Neuro-ICU	70	100	96	112	28.8	33.6	Mean hemoglobin levels at day 16 post injury	Yes	
Group 5: other patients and settings										
Prick 2014 <sup>64</sup>	Postpartum hemorrhage	S	89	74	90	22.2	27	Mean hemoglobin levels at discharge	Yes	
Webert 2008 <sup>71</sup>	Hematologic cancer	80	120	93	106	27.9	31.8	12 measurements during 30 d	Yes	

Variables in italic correspond to converted values using the following formula: hemoglobin [g/l] = hematocrit [%]/0.3.

CABG = coronary artery bypass graft; ICU = intensive care unit; IOP = not extractable (graphs only, no numerical data); NR = not reported; POP = postoperative; RCV = red cell volume; S = symptoms of anemia.

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